REMARKS

Upon entry of the above amendment, claims 1-7 and 11-15 will be pending in this application. Applicants respectfully submit that the amendment does not introduce new matter within the meaning of 35 U.S.C. §132. Accordingly, entry of the amendment is respectfully requested.

1. Rejection of Claims 16-17 under 35 U.S.C. § 102(a)

The Official Action states that claims 16 and 17 stand rejected under 35 U.S.C. §102(a) as being anticipated by Rabelnik et al. (US 6544994).

Applicants respectfully traverse this rejection. However, solely to remove the basis for this rejection, applicants have canceled claims 16-17 without prejudice to or disclaimer of the subject matter contained therein. As such, applicants respectfully request that the Examiner withdraw this rejection.

2. Rejection of claims 1-4 and 6 under 35 U.S.C. §103(a)

The Official Action states that claims 1-4 and 6 are rejected under 35 U.S.C. §103(a) over applicants own admission and Manning (US 2004/0087653) in view of Schmid et al. (WO2001/56551). In particular, the Official Action states that

> "it would have been *prima facie* obvious for a person of ordinary skill in the art to combine applicants own admission (BH4 increases the level of endogenous NO) and the teaching of Manning (Increase of endogenous NO could be beneficial for treating COPD or any other respiratory disease) with the motivation of providing a better treatment for COPD or any respiratory disease with BH4, thus resulting in the practice of claims 1-4 and 6 with a

> reasonable expectation of success as evidenced by Schmid et al. Schmid et al. teach a method useful for preventing or reversing several respiratory diseases like: ... COPD comprising the use of BH4..."

Applicants respectfully traverse this rejection. To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court recently held in *KSR International Co. v. Teleflex Inc. et al.*, 127 S. Ct. 1727, 167 L.Ed. 705 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

First, applicants respectfully draw the Examiner's attention to the claim amendments introduced in this Response and Amendment. In particular, applicants note that the transition phrase was amended to recite "consisting essentially of" instead of "comprising".

The Manning et al. reference requires the presence of an additional active agent other than a selective inhibitor of inducible nitric oxide synthase (iNOS), specifically a phosphodiesterase (PDE) inhibitor, to achieve treatment of lung disorders such as COPD. In particular, applicants note the disclosure at page 2 of the publication, paragraph [0021] which states, in relevant part, "A method for the treatment, prevention or inhibition of a respiratory disease or condition in a subject in need of such treatment, prevention or inhibition, comprising administering an iNOS inhibitor...and a phosphodiesterase (PDE) inhibitor...are described." (emphasis added) Also, at page 3 of the publication, paragraph [0035], Manning et al. state, in relevant part, "The present invention encompasses therapeutic methods using a selective iNOS inhibitor and a phosphodiesterase (PDE) inhibitor to treat, prevent or inhibit a respiratory disease or condition, and compositions therefor." (emphasis added)

Thus, the teaching of the Manning et al. reference cannot render obvious the presently claimed methods which do not require the use of a PDE inhibitor to affect treatment. As such, the Examiner has failed to establish a *prima facie* case of obviousness against the presently pending claims.

Similarly, the Schmid et al. reference teaches combination therapy of a less than therapeutic amount of BH4 and its precursors and membrane permeable cGMP analogues. As is the case with the deficient teachings of Manning et al. outlined above,

the Schmid et al. reference cannot render obvious the presently claimed methods which do not require the use of a membrane permeable cGMP analogue to affect treatment. As such, the Examiner has failed to establish a *prima facie* case of obviousness against the presently pending claims.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

3. Rejection of claims 5, 7 and 11-15 under 35 U.S.C. §103(a)

The Official Action states that claims 5, 7 and 11-15 are rejected under 35 U.S.C. §103(a) over applicants own admission and Manning (US 2004/0087653) in view of Schmid et al. (WO2001/56551) as applied to claims 1-4 and 6 above and further in view of Juturu et al. (US 2004/0097467) or Rabelnik et al. In particular, the Official Action states, in relevant part, that

> "Claim 5 recites the same limitations as claimed in claim 1, further comprising a compound selected from the group of arginine, L-arginine hydrochloride, etc...Applicant's own admission and Manning as evidenced by Schmid et al. teach all the limitations of claim 5, except for further using arginine or any of the other compounds listed in claim 5. However, Juturu et al. teach a method of treating COPD with arginine silicate inositol complex. Also Rabelink et al. teach that arginine is the precursor of endogenous NO and as a consequence it increases the production of NO... ...It would have been obvious to treat COPD or any other respiratory disease with arginine.

Applicants respectfully traverse this rejection. The requirements for establishing a *prima facie* case of obviousness are outlined above in section 2.

First, applicants respectfully remind the Examiner that the transition phrase of the

presently pending claims was amended to recite "consisting essentially of" instead of "comprising". As such, the deficiencies of the Manning et al. and Schmid et al. references which are fully outlined in section 2 above, apply to these rejected claims also.

The Juturu et al. reference discloses administration of a specific arginine-silicate-inositol complex which is not currently claimed in the rejected claims. However, the rejected claims do recite L-arginine Hydrochloride as one possible "further compound". In Figure 1 of the published application, it is clear from a reading of the data that L-arginine hydrochloride did not provide the effect that was provided by L-arginine silicate. In fact, the L-arginine hydrochloride samples in many cases did not even affect a change outside of the standard deviation of the control. Accordingly, the Juturu et al. reference in fact teaches away from using one of the specifically claimed "further compounds" recited in the presently rejected claims. As such, the Juturu et al. reference does not remedy the deficient teachings of the Manning et al. and Schmid et al. references.

Similarly, the Rabelnik et al. reference teaches combination therapy of BH4 and folic acid or a folate. As is the case with the deficient teachings of Manning et al. and Schmid et al. outlined above, the Rabelnik et al. reference cannot render obvious the presently claimed methods which do not require the use of folic acid or a folate to affect treatment. As such, the Examiner has failed to establish a *prima facie* case of obviousness against the presently pending claims.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

4. Rejection of claims 10, 18 and 23 under 35 U.S.C. §103(a)

The Official Action states that claims 10, 18 and 23 are rejected under 35 U.S.C. §103(a) over various references.

Applicants respectfully traverse these rejections. However, solely to remove the basis for these rejections, applicants have canceled claims 10, 18 and 23 without prejudice to or disclaimer of the subject matter contained therein. As such, applicants respectfully request that the Examiner withdraw this rejection.

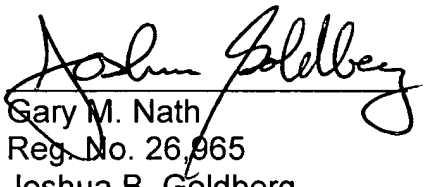
CONCLUSION

Based upon the above amendment and remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the pending rejections and allow all pending claims of this application. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,
THE NATH LAW GROUP

Date: September 16, 2008



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Appendix A

Claim Amendments

1. (Currently amended) A method for treating a respiratory disease in a patient ~~comprising~~ consisting essentially of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds to a patient in need thereof.

2. (Previously presented) The method as claimed in claim 1, wherein the respiratory disease is selected from the group consisting of COPD, bronchial asthma, pulmonary fibroses, emphysema, interstitial pulmonary disorders and pneumonias.

3. (Previously presented) The method as claimed in claim 1, wherein the respiratory disease is COPD.

4. (Currently amended) A method for treating muscular dysfunction in a COPD patient ~~comprising~~ consisting essentially of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds to a patient in need thereof.

5. (Previously presented) The method according to claim 1, wherein in addition to the compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds, a further compound selected from the group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate is used in simultaneous, separate or sequential combination with the compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds.

6. (Currently amended) A method for treating COPD in a patient ~~comprising~~ consisting essentially of the step of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds to a patient in need thereof.

7. (Previously presented) The method according to claim 6, characterized in that in addition to a therapeutically effective amount of the compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-

tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds, a therapeutically effective amount of a further compound selected from the group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate is administered in a simultaneous, separate or sequential combination with the compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds.

8. (Canceled)

9. (Canceled)

10. (Canceled)

11. (Currently amended) A method for treating a respiratory disease in a patient ~~comprising~~ consisting essentially of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds in combination with a therapeutically effective amount of a further compound selected from the group consisting of arginine, L-arginine

hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate.

12. (Previously presented) The method as claimed in claim 11, wherein the respiratory disease is selected from the group consisting of COPD, bronchial asthma, pulmonary fibroses, emphysema, interstitial pulmonary disorders and pneumonias.

13. (Previously presented) The method as claimed in claim 11, wherein the respiratory disease is COPD.

14. (Currently amended) A method for treating muscular dysfunction in a COPD patient ~~comprising~~ consisting essentially of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds, in combination with a therapeutically effective amount of a further compound selected from the group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate, to a patient in need thereof.

15. (Currently amended) A method for treating COPD in a patient ~~comprising~~ consisting essentially of the step of administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4), (6R,S)-5,6,7,8-tetrahydrobopterin, 1',2'-diacetyl-5,6,7,8-tetrahydrobopterin, Sepiapterin, 6-methyl-5,6,7,8-

tetrahydrobopterin, 6-hydroxymethyl-5,6,7,8-tetrahydrobopterin, 6-phenyl-5,6,7,8-tetrahydrobopterin, and the pharmaceutically acceptable salts of these compounds in combination with a therapeutically effective amount of a further compound selected from the group consisting of arginine, L-arginine hydrochloride (L-Arg·HCl), L-arginine acetylaspariginate, L-arginine aspartate, L-arginine citrate, L-arginine glutamate, L-arginine oxoglurate, L-arginine tidiacicate and L-arginine timonacicate.

16. (Canceled)

17. (Canceled)

18. (Canceled)

19. – 22. (Canceled)

23. (Canceled)